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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/125,751	10/30/1998	OYSTEIN FODSTAD	4885.55USWO	8143

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EXAMINER
UNGAR, SUSAN NMN

ART UNIT	PAPER NUMBER
1642	30

DATE MAILED: 08/21/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/125,751	Applicant(s) Fodstad et al
	Examiner Ungar	Art Unit 1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Jun 13, 2003* .

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1, 3, 6-8, 13-16, 18-23, and 26-28* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1, 3, 6-8, 13-16, 18-23, and 26-28* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CAR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on June 12, 2003 (Paper No. 29) is acknowledged and has been entered. Claims new claims 27 and 28 have been added An action on the RCE follows.

2 Claims 1, 3, 6-8,13-16, 18-23 and 25-28 are pending and currently under examination.

3. It is noted that Applicant's listing of the pending claims is incorrect in Paper No. 29. Claims 16 and 18 are presented as dependent upon claim 14. However, the pending claims are in actuality dependent upon claim 15.

4. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

5. The following rejections are maintained:

Claim Rejections - 35 USC § 112

6. Claims 1, 6-8, 13-14, 20-23 and 25-26 remain rejected under 35 USC 112, first paragraph for the reasons previously set forth in Paper No. 26, Section 6, pages 3-5 and new claims 27-28 are rejected under 35 USC 112, first paragraph for the reasons previously set forth in Paper No. 26, Section 6, pages 3-5.

Applicant argues that Examiner is mischaracterizing the McClaughlin reference which Examiner cites as teaching that the MOC31 antibody specifically

localizes to EGP2 on tumor cells but does not localize to normal tissues. The Mcclaughlin reference clearly suggests that the reason why the antibody does not react with normal tissue *in vivo* is due to an issue of accessibility of the antibody to those normal cells. This reference does not suggest in any way that an epitope change has occurred rendering the antibody unable to bind normal cells. The argument has been considered but has not been found persuasive because although the referenced article does not state that there has been a change of epitope, the referenced article does state that there is a limited accessibility of the EGP2 on normal cells as compared to tumor cells. Is this increased accessibility only to MOC31, is it accessibility to all antibodies against EGP2, is it due to increased expression of EGP2 in tumor as opposed to normal cells? Is it due to an altered conformation of EGP2 which results in a newly exposed epitope? Is it due to an alteration in cell structure, which results in the exposure of an epitope, is there a change in the matrix surrounding the cell? Although Applicant hypothesizes that the good efficacy of MOC31 is due to increased expression of EPG2, neither the specification, nor the art of record suggests that this is the case and Applicant has not provided objective evidence that would suggest that the broadly claimed anti EPG2 antibodies will function as claimed. Applicant is invited to submit objective evidence demonstrating that EGP2 is overexpressed in tumor cells compared to normal cells and that antibodies other the claimed antibody will function as claimed. In addition, Applicant appears to be confused when discussing the McClaughlin reference in regard to MUC1 antibody since the McClaughlin reference is dawn to MOC31, the EPG-2 antibody, not to a MUC1 antibody. Applicant goes on to

present evidence demonstrating that MOC31 binds to normal cells as well as to tumor cells. A review of Engerbraaten al reveals that the MOC31 binding to normal cells described appears to be binding that occurs *in vitro*. However, McClaughlin et al clearly state that no *in vivo* localization to normal tissue was found with the MOC31 antibody. The differences between *in vivo* and *in vitro* binding conditions are well known in the art. For example, *in vitro* assays cannot duplicate the complex conditions of *in vivo* therapy. In the assays, the antibody is in contact with cells during the entire exposure period. This is not the case *in vivo*, where exposure at the target site may be delayed or inadequate. It is clear that the teaching of the Engerbraaten reference is not commensurate in scope with the claimed invention. Although DeLeij et al state that normal cells are reactive with anti-EGP-2 antibodies, only the first page of the reference is presented and although the reference refers to other references in support of this finding, these references were not submitted and there is no way to determine if this data was secured using *in vivo* or *in vitro* data, or whether MOC31 was used and found to bind differentially to normal or tumor cells when compared to other anti-EPG-2 antibodies. Again in view of the teachings of McClaughlin et al, it is not possible to evaluate the teachings of DeLeij et al. Further, Applicant submits Bergsagel et al to support the expression of a murine homologue mRNA of human EGP. The relevance of this reference to the instant application is unclear. A review of the face page of Szala et al, does not lend support to the enablement of the claimed invention. It is unclear why applicant is not submitting the entire reference for consideration. A review of the Strnad et al reference again reveals that there is no way to determine if the data drawn to

antibody binding to KS1/4 was secured using *in vivo* or *in vitro* techniques. Further, no evidence is presented that KS1/4 is the EGP-2 of the instant application. Kosterink et al present data drawn to imaging patients with radioactivity labeled MOC31 which teaches that MOC31 is known to bind to normal cells. The teaching of Kosterink et al is not persuasive. A review of the cited reference at page 2361 column 2, as well as figure 6, reveals that the apparent uptake of the indium-labeled antibody in spleen, bone marrow and liver is an effect frequently seen with indium-labeled antibodies. Although the reference speculates that the uptake in kidneys may be antigen-related uptake, the reference also speculates that the uptake seen could as easily be from clearance of indium containing low molecular weight conjugates. Uptake in the small intestine and colon is speculated to be uptake in the fecal stream which is known to occur with indium labeled antibodies. The reference concludes that although MOC-31 stains normal epithelial on tissue sections *in vitro*, normal epithelial prove to be poorly accessible to MOC-31 in vivo. The reference goes on to speculate why the epitope that MOC31 binds to *in vitro* is poorly accessible *in vivo*. The reference does not suggest that the increased accessability of tumor to MOC31 compared to normal controls is due to increased expression of the antigen, does not suggest that other antibodies would also have increased accessibility to tumors as compared to normal controls. Thus, for the reasons of record, it would require undue experimentation for one of skill in the art to practice the broadly claimed invention.

Further, as drawn to the BM2 and BM7 antibodies, Applicant submits two descriptions of the reactivity of the BM7 and BM2 antibodies in German. It is not

possible for Examiner to evaluate the submitted references since they were not submitted in the English language.

Given the surprising nature of the invention, as specifically disclosed by Applicant, it cannot be predicted from the information in either the specification or the art of record whether the invention as broadly claimed will function as claimed.

Finally, Applicant submits that MOC31 has been run through a Phase 1 study for acceptance as a medicament and a copy of the clinical protocol is enclosed at attachment 5. In view of the submissions, Applicant argues that the claimed invention is used in a method for treatment. The argument has been considered but has not been found persuasive, as there has been no submission of any evidence that the MOC31 antibody can be used for anything other than research purposes. Clearly a Phase 1 study is for research purposes only. Applicant has not suggested or produced any evidence that suggests that the MOC31 antibody can be used for anything other than research or that it can be used as a medicament. All the proposal says is that the MOC31 antibody is a research tool.

Applicant is invited to submit objective evidence demonstrating MOC31 can be used as a medicament and that the surprising result seen with the MOC31 antibody can also be duplicated by the broadly claimed anti-EPG-2 antibodies. Applicants arguments have not been found persuasive and the rejection is maintained.

7. Claims 3, 15, 16, 18, 19 remain rejected under 35 USC112, first paragraph for the reasons previously set forth in paper No. 26, Section 5, pages 6-7.

Applicant requests that the rejection be held in abeyance pending the deposit

and submission of appropriate documentation regarding the deposit of BM2 antibody with ATCC. In view of Applicant's arguments, the rejection is maintained but held in abeyance pending submission of the appropriate documentation and appropriate amendment of the specification and claims regarding the deposit information.

8. Claims 3, 15, 16, 18, 19 remain rejected under 35 USC 112, second paragraph for the reasons previously set forth in Paper No. 26, section 8, pages 8-9.

Applicant requests that the rejection be held in abeyance pending the deposit and submission of appropriate documentation regarding the deposit of BM2 antibody with ATCC. In view of Applicant's arguments, the rejection is maintained but held in abeyance pending submission of the appropriate documentation and appropriate amendment of the specification and claims regarding the deposit information.

Claim Rejections - 35 USC § 103

9. Claims 1, 13, 14 24 remain rejected under 35 USC 103 for the reasons previously et forth in Paper No. 26, Section 9, page 9.

Applicant argues that the specification provides several exemplary instances of unexpected synergy between BM7 and MOC31, and BM2 and MOC 31, and one skilled in the art would reasonably expect that different immunotoxins directed to the same antigens would also produce the surprising and unexpected results shown by the inventors. The argument has been considered but has not been found persuasive because Applicant is arguing limitations not recited in the claims as currently constituted and for the reasons previously set forth, the invention as

claimed is *prima facie* obvious. The arguments have not been found persuasive and the rejection is maintained.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

10. Claims 27 and 28 are rejected under 35 USC 112, first paragraph as failing to provide an adequate written description of the invention and failing to provide an enabling disclosure because the specification does not provide evidence that the claimed biological material is (1) known and readily available to the public, (2) reproducible from a written description or (3) deposited for the reasons previously set forth drawn to the deposit of antibody BM7 recited in Paper No. 13, mailed April 5, 2000.

Since Applicant has requested that the rejection be held in abeyance pending submission of the appropriate documentation and appropriate amendment of the specification and claims regarding the deposit information of antibody BM7, this rejection will be held in abeyance.

11. Claims 27-28 are rejected under 35 USC 112, second paragraph for the reasons previously set forth drawn to the indefinite nature of the recitation of antibody BM7.

Since Applicant has requested that the rejection be held in abeyance pending submission of the appropriate documentation and appropriate amendment of the specification and claims regarding the deposit information of antibody BM7, this rejection will be held in abeyance.

12. All other objections and rejections recited in Paper No. 26 are withdrawn.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Unbar, P.d. whose telephone number is (703) 305-2181. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached at (703) 308-3995. The fax phone number for this Art Unit is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Effective, February 7, 1998, the Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1640.

Susan Unbar
Primary Patent Examiner
August 11, 2003